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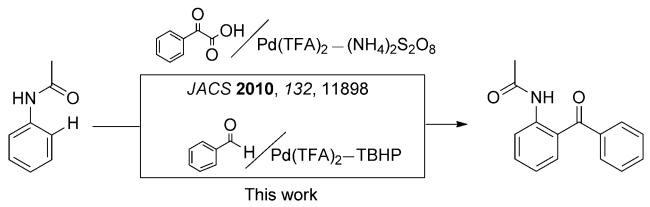
Palladium-Catalyzed *ortho*-Acylation of Acetanilides with Aldehydes through Direct C–H Bond Activation

Chengliang Li,[a] Lei Wang,*[a, b] Pinhua Li,*[a] and Wei Zhou[a]

Transition-metal-catalyzed direct C–H bond functionalization, one of the hot topics in current organic chemistry, represents a burgeoning field because it enables the efficient construction of carbon–carbon or carbon–heteroatom bonds without the use of stoichiometric organometallic coupling reagents. Since the discovery of σ-chelation directed C–H bond activation,[1] extensive efforts have been made in this field.[2] The combination of transition metals and directing groups is a useful strategy to facilitate C–H bond cleavage, which affords valuable transformations of C–H bonds to other covalent bonds. Among them, palladium-mediated C–H activation is one of the most attractive processes.[3] In this area of research, various functional groups containing heteroatoms, such as acyl/acyloxy,[4] pyridyl,[5] oxazolyl,[6] *N*-methoxy carbamoyl,[7] and acetoamino groups can provide an anchor for either stoichiometric or catalytic *ortho*-metalation of aromatic rings. With the acetamino group as a directing group, the *ortho* C–H bond of acetanilide can be highly regioselectively functionalized. Horino and co-workers have reported the *ortho*-vinylation of acetanilides through cyclopalladation complexes in 1981,[8] and Tremont have described the Pd^{II}-promoted direct functionalization of acetanilides with alkyl iodides in 1984.[9] Recently, significant progress in this area has been achieved with a variety of coupling partners.[10]

o-Acylacetanilides are important structural units and synthetic intermediates in biologically active natural products and medicinal chemistry.[11] For their potential application, the development of convenient synthetic pathway is highly desirable. In 2010, Ge and co-workers have developed the decarboxylative *ortho*-acylation of acetanilides with α-oxocarboxylic acids through palladium-catalyzed C–H activation to prepare *o*-acyl acetanilides.[10a] Inspired by the recent studies of direct functionalization of acetanilides, we would like to realize the palladium-catalyzed *ortho*-acylation of acetanilides with commercially available, inexpensive aldehydes through direct C–H bond activation. It is worth noting that there are only a few examples of the transition-metal-catalyzed direct access to ketones from aldehydes through C–H cleavage of arenes.[12] To our pleasure, we have achieved this assumed process. Herein, we will describe the palladium-catalyzed *ortho*-acylation of acetanilides with aldehydes in the presence of *tert*-butyl hydroperoxide (TBHP) as the ideal oxidant, affording the *o*-acyl acetanilides in moderate to good yields (Scheme 1).



Scheme 1.

Our initial investigation focused on the effect of a transition-metal catalyst on the *ortho*-acylation of acetanilides with aldehydes. Several palladium, nickel, and iron sources were screened in a model reaction of acetanilide (**1a**) with *para*-chlorobenzaldehyde (**2e**), and the results are summarized in Table 1. The *ortho*-acylation reaction of acetanilide could be catalyzed by Pd^{II} salts, Pd^{II}, or Pd^{0} complexes, such as $Pd(CF_3CO_2)_2$, $Pd(OAc)_2$, $PdCl_2$, $[Pd(PPh_3)_2Cl_2]$, $[Pd(PCy_3)_2Cl_2]$, $[Pd(CH_3CN)_2Cl_2]$, or $[Pd(PPh_3)_4]$ in the presence of *tert*-butyl hydroperoxide (TBHP) in toluene. It is evident that $Pd(CF_3CO_2)_2$ was the most effective catalyst for the reaction (Table 1, entries 1–7);[10a] probably the *ortho*-acylation of acetanilide requires a highly cationic Pd^{II} species to facilitate the formation of palladacycle intermediate through the electrophilic substitution of arene,[13] and the dissociation of $Pd(CF_3CO_2)_2$ to a trifluoroacetate anion and a cationic Pd^{II} species is easier than that of $Pd(OAc)_2$.[4c,14] But, Pd/C, $Ni(acac)_2$, $Fe(acac)_3$, $FeCl_3$, and $FeBr_2$ failed to facilitate the reaction (Table 1, entries 8–12). A variety of oxidants were examined for their effect on the model reaction and the results were also shown in Table 1. To our delight, the model reaction proceeded smoothly and generated the desired product in 80% yield, representing one of the

[a] C. Li, Prof. Dr. L. Wang, Dr. P. Li, W. Zhou
Department of Chemistry, Huaibei Normal University
Huaibei, Anhui 235000 (P.R. China)
Fax: (+86) 561-3090518
E-mail: leiwang@chnu.edu.cn
pinhuali@yahoo.com.cn

[b] Prof. Dr. L. Wang
State Key Laboratory of Organometallic Chemistry
Shanghai Institute of Organic Chemistry
Shanghai 200032 (P. R. China)

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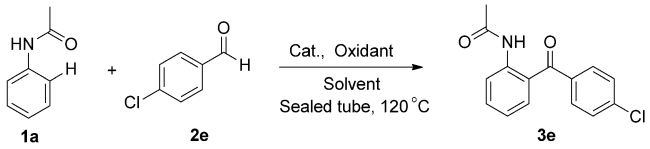
Table 1. Screening of catalysts, oxidants and solvents for the palladium-catalyzed *ortho*-acylation of acetanilide with *para*-chlorobenzaldehyde.[a]



1a 2e 3e

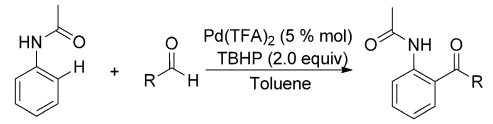
Entry	Catalyst	Oxidant	Solvent	**3e** [%][b]
1	$Pd(CF_3CO_2)_2$	TBHP	toluene	80
2	$Pd(OAc)_2$	TBHP	toluene	66
3	$[Pd(PPh_3)_2Cl_2]$	TBHP	toluene	33
4	$[Pd(PCy_3)_2Cl_2]$	TBHP	toluene	17
5	$[Pd(CH_3CN)_2Cl_2]$	TBHP	toluene	34
6	$[Pd(PPh_3)_4]$	TBHP	toluene	38
7	$PdCl_2$	TBHP	toluene	35
8	Pd/C	TBHP	toluene	N.R.
9	$Ni(acac)_2$	TBHP	toluene	N.R.
10	$Fe(acac)_3$	TBHP	toluene	N.R.
11	$FeCl_3$	TBHP	toluene	N.R.
12	$FeBr_2$	TBHP	toluene	N.R.
13	$Pd(CF_3CO_2)_2$	$(tert\text{-}C_4H_9O)_2$	toluene	39
14	$Pd(CF_3CO_2)_2$	DCP	toluene	37
15	$Pd(CF_3CO_2)_2$	$(C_6H_5COO)_2$	toluene	N.R
16	$Pd(CF_3CO_2)_2$	DDQ	toluene	N.R
17	$Pd(CF_3CO_2)_2$	$C_6H_5I(OAc)_2$	toluene	N.R.
18	$Pd(CF_3CO_2)_2$	$K_2S_2O_8$	toluene	N.R.
19	$Pd(CF_3CO_2)_2$	CF_3CO_2Ag	toluene	N.R.
20	$Pd(CF_3CO_2)_2$	Ag_2O	toluene	N.R.
21	$Pd(CF_3CO_2)_2$	$CuSO_4$	toluene	N.R.
22	$Pd(CF_3CO_2)_2$	$KBrO_3$	toluene	N.R.
23	$Pd(CF_3CO_2)_2$	O_2	toluene	N.R.
24	$Pd(CF_3CO_2)_2$	I_2	toluene	N.R.
25	$Pd(CF_3CO_2)_2$	TBHP	C_6H_5Cl	55
26	$Pd(CF_3CO_2)_2$	TBHP	benzene	36
27	$Pd(CF_3CO_2)_2$	TBHP	DCE	16
28	$Pd(CF_3CO_2)_2$	TBHP	DMF	N.R.
29	$Pd(CF_3CO_2)_2$	TBHP	DMSO	N.R.
30	$Pd(CF_3CO_2)_2$	TBHP	NMP	N.R.
31	$Pd(CF_3CO_2)_2$	TBHP	dioxane	N.R.
32	$Pd(CF_3CO_2)_2$	TBHP	THF	N.R.
33	$Pd(CF_3CO_2)_2$	TBHP	C_2H_5OH	N.R.
34	$Pd(CF_3CO_2)_2$	TBHP	diglyme	N.R.
35	$Pd(CF_3CO_2)_2$	TBHP	CH_3CN	N.R.

[a] Reaction conditions: acetanilide (1.0 equiv), *para*-chlorobenzaldehyde (1.5 equiv), catalyst (0.05 equiv), oxidant (2.0 equiv), solvent (1.5 mL mmol^{-1}), sealed tube, 120 °C, under air, 24 h. [b] acac = acetylacetonate, DCP = dicumyl peroxide, DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone, TBHP = *tert*-butyl hydroperoxide, DCE = 1,2-dichloroethane, DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide, NMP = *N*-methyl-2-pyrrolidone. [d] Yields of isolated products after flash chromatography.

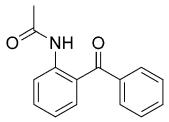
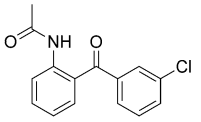
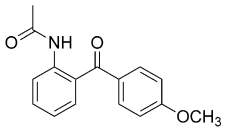
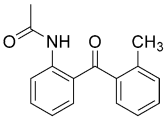
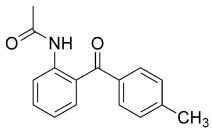
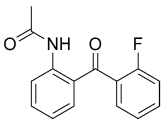
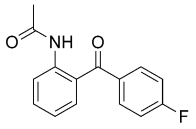
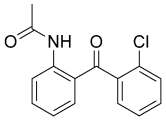
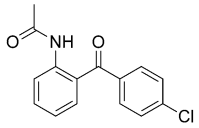
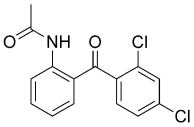
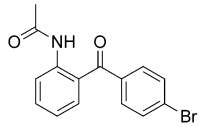
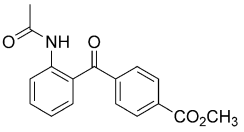
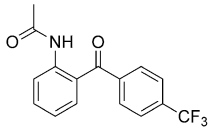
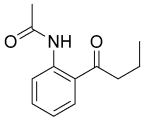
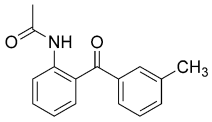
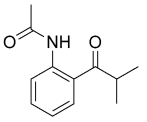
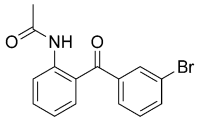
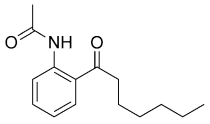
best results when 2 equiv of TBHP was used as oxidant (Table 1, entry 1). It was found that $(t\text{-}C_4H_9O)_2$ and dicumyl peroxide (DCP) were much more inferior oxidants and generated the desired product in 39 and 37% yields, respectively (Table 1, entries 13 and 14). Unfortunately, other oxidants, such as $(C_6H_5COO)_2$, DDQ, $C_6H_5I(OAc)_2$, $K_2S_2O_8$, CF_3CO_2Ag, Ag_2O, $CuSO_4$, $KBrO_3$, O_2, and I_2 were no longer effective oxidants in this reaction and no desired product was isolated (Table 1, entries 15–24). With respect to the oxidant loading, 2 equiv of TBHP was found to be optimal; when less than 2 equiv of TBHP was used, the reaction did not go to completion; however, no significant improvement was observed with more 2 equiv of TBHP. The effect of solvent on the reaction was also investigated; among the solvents tested, toluene was the most suitable reaction media for the *ortho*-acylation reaction of acetanilide. Chlorobenzene, benzene, and 1,2-dichloroethane were inferior and generated **3e** in 56, 36 and 16% yields, respectively (Table 1, entries 25–27). Unfortunately, no desired product was isolated when the reactions were carried out in DMF, DMSO, NMP, dioxane, THF, C_2H_5OH, diglyme, or CH_3CN (Table 1, entries 28–35). During the course of further optimization of the reaction conditions, the reaction was generally completed within 24 h when it was performed at 120 °C by using 5 mol% of $Pd(CF_3CO_2)_2$ in the presence of TBHP (2 equiv) in toluene. Meanwhile, when the model reaction was carried out at 100 °C and 150 °C, the desired product **3e** was isolated in 45 and 32% yields, respectively.

With the optimized conditions in hand, the scope of the Pd-catalyzed *ortho*-acylation of acetanilides with aldehydes through direct C–H bond activation was investigated with a variety of aldehydes. The results are summarized in Table 2. As can be seen from Table 2, the reactivity of both aliphatic and aromatic aldehydes was observed, with the aromatic aldehydes shown to be much more reactive than aliphatic ones (Table 2, **3a–3o** vs. **3p–3r**). The aromatic aldehydes displayed high reactivity under the present reaction conditions and good yields of desired *ortho*-acylation of acetanilide products were obtained. Aromatic aldehydes with both electron-donating and electron-withdrawing functionalities, such as methoxy, methyl, trifluoromethyl, fluoro, chloro, bromo, and CO_2CH_3 groups, afforded the corresponding isolated products in yields of 63–86% (Table 2, **3b–3o**). As one of the substrates, an aromatic aldehyde with a methyl group at the *meta* position of the phenyl ring (compound **3h**) gave a comparable product yield to that of benzaldehyde (**3a**). Meanwhile, an aromatic aldehyde with a methyl group at the *para* position of the phenyl ring (**3c**) gave a superior product yield to that of benzaldehyde (**3a**), and aromatic aldehyde with a methyl group at the *ortho* position of the phenyl ring (compound **3k**) gave inferior product yield to that of benzaldehyde (**3a**). This *ortho*-position effect has also been observed in the reaction of 2-fluorobenzaldehyde or 2-chlorobenzaldehyde as one of the substrate (**3l** and **3m**). It is known that *ortho* substitution on the phenyl rings hampers the Pd-catalyzed C–H insertion at *ortho* position, displaying the obvious "*ortho*-substituent" effect.[10g, n, 15] It is important to note that aromatic aldehydes with an electron-withdrawing group, such as trifluoromethyl, fluoro, chloro and bromo group at the *para* position of the phenyl ring, afforded a better yield than that of benzaldehyde (**3d–3g** vs. **3a**). Moreover, substrate with the strong electron-donating methoxy group at the *para* position of the phenyl ring (compound **3b**) delivered a lower yield than its counterparts substituted by the methyl group (**3b** vs. **3c**). When both the *ortho*- and *para* positions of the phenyl ring were occupied by a chloro group, the product yield was comparable to that

Table 2. The scope of aldehydes in palladium-catalyzed *ortho*-acylation of acetanilides with aldehydes.[a]



1a 3a–3r

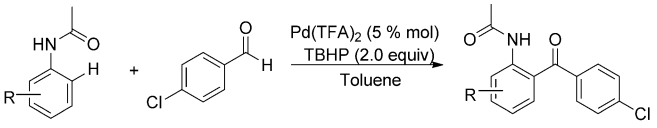
Product	3	Yield [%][b]	Product	3	Yield [%][b]
	**3a**	73		**3j**	71
	**3b**	74		**3k**	68
	**3c**	78		**3l**	65
	**3d**	82		**3m**	63
	**3e**	80		**3n**	71
	**3f**	74		**3o**	67
	**3g**	86		**3p**	64
	**3h**	72		**3q**	57
	**3i**	75		**3r**	60

[a] Reaction conditions: acetanilide (1.0 mmol), aldehyde (1.5 mmol), Pd(CF_3CO_2)$_2$ (0.05 mmol), TBHP (2.0 mmol), toluene (1.5 mL), sealed tube, 120 °C, under air, 24 h. [b] Yields of isolated products after flash chromatography.

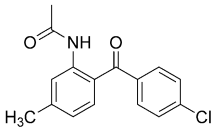
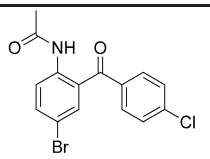
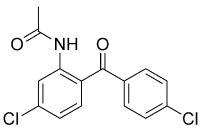
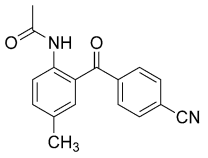
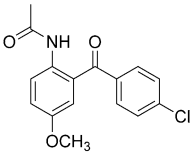
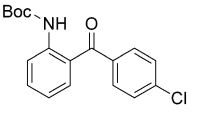
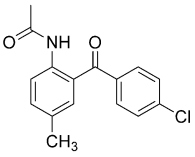
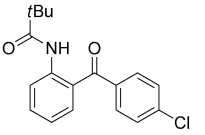
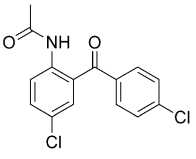
of benzaldehyde (**3a** vs. **3n**) due to the combination of electronic effect and steric hindrance. Fortunately, the aliphatic aldehydes, such as *n*-butyraldehyde, *iso*-butyraldehyde and *n*-heptaldehyde, also reacted with acetanilide smoothly under present reaction conditions and 57–64% isolated yields of the desired products **3p**–**3r** were obtained, respectively (Table 2).

To expand the scope of acetanilide, a diverse array of substituted acetanilides were surveyed. The substituted acetanilides, with either electron-donating or electron-withdrawing groups on the benzene rings of acetanilides, could be applied to afford the desired products **3s**–**3y** in good yields (Table 3). The similar phenomenon has also been observed in the *ortho*-acylation of substituted acetanilides with *p*-chlorobenzaldehyde. A substituted acetanilide with a methyl group at the *meta*- or *para* position of the benzene ring gave comparable product yields to that of acetanilide (Table 3, **3s** and **3v** vs. **3e**). At the same time, substituted acetanilides with a weak electron-withdrawing group, such as chloro or bromo group at the *para*- or *meta* position of the benzene ring, also afforded a comparable product yield to that of acetanilide (Table 3, **3t**, **3w** or **3x** vs. **3e**). On the other hand, substituted acetanilides with a strong electron-donat-

Table 3. The scope of acetanilides in palladium-catalyzed *ortho*-acylation of substituted acetanilides with *para*-chlorobenzaldehyde.[a]



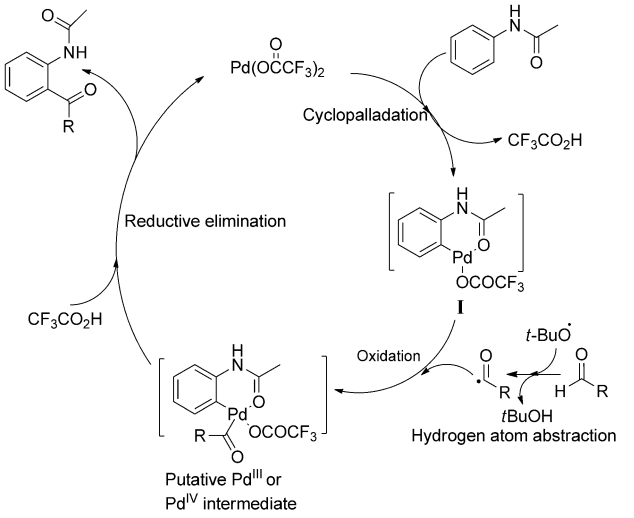
2e 3s–3aa

Product	3	Yield [%][b]	Product	3	Yield [%][b]
	**3s**	80		**3x**	75
	**3t**	71		**3y**	68
	**3u**	67		**3z**	trace
	**3v**	80		**3aa**	trace
	**3w**	71			

[a] Reaction conditions: substituted acetanilide (1.0 mmol), *para*-chlorobenzaldehyde (1.5 mmol), Pd(CF_3CO_2)$_2$ (0.05 mmol), TBHP (2.0 mmol), toluene (1.5 mL), sealed tube, 120 °C, under air, 24 h. [b] Yields of isolated products after flash chromatography.

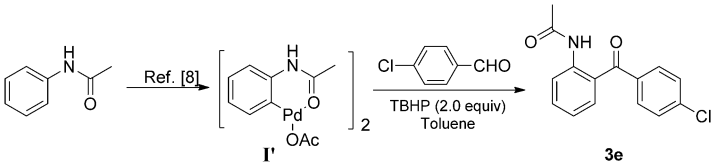
ing methoxy group at the *para* position of the benzene ring afforded an inferior yield to that of the unsubstituted one (Table 3, **3u** vs. **3e**). It should be noted that the substrates without symmetry, such as *meta*-methylacetanilide and *meta*-chloroacetanilide, underwent the regiospecific *ortho*-acylation to generate **3s** and **3t**, respectively, because of the steric effect. Other anilides, except for acetanilide, were also examined. Regrettably, *tert*-butyl phenylcarbamate and *N*-phenylpivalamide reacted with *para*-chlorobenzaldehyde under the recommended reaction conditions in much lower reactivity and only trace amounts of the desired products (Table 3, compounds **3z** and **3aa**) were detected by TLC, owing to the steric hindrance of *tert*-butoxycarbonyl and pivalyl groups.

A plausible mechanism of the palladium-catalyzed *ortho*-acylation of acetanilide with aldehyde through direct C–H bond activation is depicted in Scheme 2. The reaction occurs probably involving 1) the formation of a cyclopalladated intermediate (**I**) by chelate-directed C–H activation of the



Scheme 2. Possible mechanism of the palladium-catalyzed *ortho*-acylation of acetanilide with aldehyde.

benzene ring of acetanilide with $Pd(CF_3CO_2)_2$;[8,9] 2) the reaction of obtained **I** with the acyl radical, which was generated in situ by hydrogen-atom abstraction of the aldehyde, forming either reactive Pd^{IV}[16] or the dimeric Pd^{III}[17] intermediate; and finally, 3) carbon–carbon bond formation through reductive elimination affording the *ortho*-acylation of acetanilide product and regenerating the Pd^{II} species for the next run. A very similar prepared palladacycle **I′** dimer could stoichiometrically transform to the *ortho*-acylation product **3e** under the present reaction conditions (Scheme 3), which offered a further proof for this proposed mechanism.[8,10c,i,k,18] It should



Scheme 3.

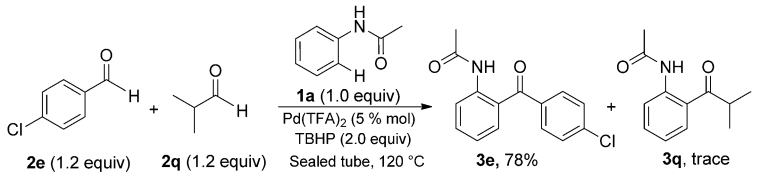
be noted that the catalytic C–H acylation was suppressed by radical scavenger, such as ascorbic acid in a dose-dependent manner.[19]

We also tried the competitive *ortho*-acylation of acetanilide between the aromatic aldehyde and aliphatic aldehyde. The results indicated that 78% yield of **3e** was isolated and only a trace amount of **3q** was detected when acetanilide underwent *ortho*-acylation with 2-chlorobenzaldehyde and *iso*-butyraldehyde under the present reaction conditions (Scheme 4). It also supports the possible mechanism in Scheme 2 because the stability of benzoyl radical is more than that of butyryl radical.

In summary, an efficient approach for the direct *ortho*-acylation of acetanilides has been developed based on a palladium catalyzed C–H activation process. This novel method provides easy access to *o*-acyl acetanilides by direct *ortho*-acylation of acetanilides using the commercially available, inexpensive aromatic and aliphatic aldehydes as the acylation reagents for C–H bond functionalization in the presence of *tert*-butyl hydroperoxide (TBHP) as the ideal oxidant, affording the *o*-acyl acetanilides in good yields. Further investigation on the application of this kind of catalyst in asymmetric catalysis is underway in our laboratory.

Experimental Section

General procedure: Under an air atmosphere, a sealable reaction tube equipped with a magnetic stir bar was charged with acetanilide (1.0 mmol), aldehyde (1.5 mmol), $Pd(CF_3CO_2)_2$ (0.05 mmol), TBHP (2.0 mmol) and toluene (1.5 mL). The rubber septum was then replaced by a Teflon-coated screw cap, and the reaction vessel placed in an oil bath at 120 °C. After stirring the mixture at this temperature for 24 h, it was cooled to room temperature and diluted with dichloromethane. The resulting solution was directly filtered through a pad of silica gel using a sintered glass funnel, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluant: hexane/ethyl acetate = 3:1, v/v) to give the desired *ortho*-acylation product. The identity and purity of known products was confirmed by ^1H and ^{13}C NMR spectroscopic analysis and the new products were fully characterized. See the Supporting Information for full details.



Scheme 4. The competitive *ortho*-acylation of acetanilide between 2-chlorobenzaldehyde and *iso*-butyraldehyde.

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Keywords: acetanilides · aldehydes · C–H activation · palladium · synthetic methods

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